DEPARTMENT OF HEALTH & HUMAN SERVICES d1503b Public Health Service

Food and Drug Administration
Rockville MD 20857

March 26, 1998

Transmitted Via Facsimile

Steven C. Quay, M.D., Ph.D.
President
Sonus Pharmaceuticals, Inc.
22026 20th Avenue S.E., Suite 102
Bothell, Washington 98021

RE: NDA 20-737
EchoGen (perflenapent) Emulsion
MACMIS # 6003

WARNING LETTER

Dear Dr. Quay:

This Warning Letter concerns Sonus Pharmaceuticals, Inc.'s (Sonus) promotional materials (labeling and advertising) for EchoGen (perflenapent) Emulsion. As you know, EchoGen is an investigational new drug that has not been approved for marketing by the Food and Drug Administration (FDA). However, as part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has obtained materials distributed by Sonus that state or suggest that EchoGen is a safe and effective ultrasound contrast agent for echocardiography and radiology imaging. Based on these materials, we have concluded that Sonus is disseminating promotional materials for EchoGen that constitute pre-approval promotion and that contain statements or suggestions that are false or misleading in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 355(a), 352(a), 331(a), 331(d), and applicable regulations.

A. Promotion of an Investigational New Drug

Under 21 CFR § 312.7, a sponsor or investigator, or any person acting on behalf of a sponsor or investigator, "shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug...." As described below, the materials disseminated by Sonus clearly are promotional in tone and contain promotional claims, including comparative claims that promote

the alleged safety and effectiveness of EchoGen. These activities constitute pre-approval promotion of an investigational new drug.

These promotional messages are false, misleading, or inconsistent with respect to the uses, if any, that may ultimately be approved and the relative safety and effectiveness related to those uses. Thus, Sonus does not know what indications and other information the final product labeling will contain if the product is ultimately approved.

Additionally, Sonus' representations about the drug are overly optimistic. Such representations exaggerate the effectiveness and minimize the risk with respect to such investigational drugs. Based on the information Sonus submitted to the agency, the dissemination of these messages raise significant public health concerns because health care providers who receive these messages may retain false or misleading impressions about the uses of EchoGen. Such misimpressions could result in widespread misuse if the product is ever approved for commercial distribution.

B. Sonus' Promotional Activities

Sonus' activities represent a highly organized and orchestrated campaign to promote EchoGen, an investigational new drug. The promotional materials include, among other items, the following:

1. Advertisements and articles published in a Sonus sponsored supplement to Applied Radiology, "Emergence of Contrast Ultrasound: A New Modality in Diagnostic Radiology," October 1997.

2. Advertisements and articles published in a Sonus sponsored supplement to Clinical Cardiology, "A New Generation of Ultrasound Contrast Agents for Echocardiography," October 1997.

3. A slide kit distributed by Sonus titled "Advancing the Image of Ultrasound."

4. Information presented by Sonus on its Internet World Wide Web site.

Both of the journal supplements sponsored by Sonus, contain an advertisement about the use of an ultrasound contrast agent by Sonus and an ad for EchoGen by Abbott, Sonus' marketing partner. EchoGen is discussed in the "Introduction" to

each supplement and is either mentioned in, or is the subject of, all of the articles in the supplements. In addition, each supplement contains an article by Sonus' President and CEO. Sonus distributed the Applied Radiology supplement and the slide kit at its exhibit hall booth to attendees of the Radiological Society of North America Annual Meeting in Chicago, December, 1997, and the Clinical Cardiology supplement at its exhibit hall booth to attendees of the American Heart Association 70th Scientific Meeting in Orlando, October 1997. In addition, in November, 1997, Sonus provided detailed information about the alleged safety and effectiveness of EchoGen on its Internet World Wide Web (WWW) site. Although EchoGen is an investigational new drug, the materials distributed by Sonus state or suggest that EchoGen is safe and effective for a variety of uses and that it is superior to other ultrasound contrast agents.

Materials and activities that claim or represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation, or that otherwise promote the drug, are violative. Sonus' violative promotional activities are further described below.

1. Advertisements

The advertisements on the inside covers of the supplements to Applied Radiology and Clinical Cardiology promote unapproved uses for EchoGen. The focus of the advertisements are on enhancing ultrasound imaging with a contrast agent. The ad presents before and after ultrasound contrast images of (1) carotid artery, (2) cardiac function, (3) hemangioma, (4) myocardial perfusion, (5) renal artery stenosis, and (6) lower extremity bypass graft. These images and image captions state or suggest claims of effectiveness for each of the uses shown. Although EchoGen is not specifically named in these ads, as discussed above, the supplements are sponsored by Sonus, all of the articles in the supplements focus on or discuss the attributes of EchoGen, and EchoGen is named on the back cover of the supplement in Abbott advertisements.

2. Supplement to Applied Radiology

Sonus sponsored the publication of a supplement to Applied Radiology, and then distributed the supplement to health care providers. The Sonus sponsored supplement contains several articles that discuss the safety and effectiveness of EchoGen as an ultrasound contrast agent. For example:

- The article by Barry Goldberg, M.D., "Role of Contrast agents in ultrasonography," states that EchoGen (1) has both radiologic and echocardiographic applications; (2) aids in visualization of the entire length of the renal artery and vein; (3) aids in visualization of intrahepatic branches of the portal vein and hepatic artery; (4) data suggest the potential use of EchoGen emulsion to aid in the characterization of hepatic lesions; and, (5) produces enhancement of the myocardium on an echocardiogram, permitting assessment of myocardial perfusion.

- The article by Laurence Needleman, "Review of a new ultrasound contrast agent - EchoGen emulsion," describes the use of EchoGen for facilitating the visualization of anatomic structures, lesions, and blood flow patterns during studies of the liver, kidney, and peripheral vasculature. The article also states that "EchoGen emulsion was shown to facilitate visualization of blood flow and structures, and significantly impact diagnosis and patient management."

- The article by Jean-Michel Correas, M.D., et al., "Current assessment of renal ultrasound and the future role of contrast enhancement," describes the use of EchoGen for use in patients with a high risk of renal artery stenosis, and for evaluating graft status in renal allografts. Dr. Correas further describes the use of ultrasound "for detection of renal cell carcinoma in cases of large masses (greater than 2 cm), and especially for identifying involvement in the retrohepatic inferior vena cava segments." The article also contains an EchoGen-aided ultrasound image of a small adenocarcinoma and states or suggests that EchoGen is effective in the identification of small adenocarcinomas.

- The article by Steven Quay [President and CEO of Sonus] et al., "Safety evaluation: Contrast ultrasound with perflenapent emulsion in radiography and echocardiography," states the authors' criteria for the "ideal ultrasound contrast agent" and concludes that EchoGen fulfills these criteria.

3. Supplement to Clinical Cardiology

Sonus sponsored the publication of a supplement to Clinical Cardiology titled "A New Generation of Ultrasound Contrast Agents for Echocardiography." Sonus distributed this supplement at its booth at the American Heart Association's 70th Scientific Meeting in Orlando, October 1997. The supplement contains several articles that include claims of safety and effectiveness for EchoGen. For example:

- The article "Perflenapent Emulsion (EchoGen): A New Long-Acting Phase-Shift Agent for Contrast Echocardiography" by Paul Grayburn, contains extensive claims of effectiveness of EchoGen, including some claims that are attributed to "(Data on file, SONUS Pharmaceuticals)." Some of these claims are:

  1. "Proposed indications for perflenapent emulsion include (1) use in echocardiography to provide contrast enhancement of ventricular chambers and improve endocardial border delineation in adult patients undergoing ventricular function and wall motion studies with suboptimal echoes, (2) use in the assessment of myocardial perfusion in adults to provide myocardial tissue enhancement of the left ventricular wall, and (3) Doppler signal enhancement. (Data on file, SONUS Pharmaceuticals.)"

  2. "In a phase III trial of 254 patients, perflenapent emulsion resulted in intermediate or full left ventricular opacification in 83% of patients, compared with 54% with sonicated albumin. This comparative study showed that perflenapent emulsion also increased duration of opacification; provided a superior contrast imaging window; improved endocardial border delineation; improved echocardiograms from suboptimal to diagnostically useful; enhanced color Doppler and spectral Doppler; facilitated assessment of wall motion; increased myocardial opacification; increased gray-scale level in the myocardium; disclosed new diagnostic findings; eliminated the need for additional studies; assisted clinicians in reaching a diagnosis; and improved the investigator's confidence in the diagnosis." (Comparative percentages omitted).

  3. "Perflenapent also improved the echocardiographic assessment of left ventricular volumes and ejection fraction...."

  4. "Perflenapent emulsion can also improve harmonic and power-mode Doppler imaging."

  5. "Other contrast agents are not as convenient. For example, sonicated albumin (Albunex...) needs refrigeration before use...."

  6. Perflenapent emulsion "should significantly aid in the diagnosis of valvular lesions, hemodynamic alterations, pulmonary hypertension, and left ventricular diastolic function;" Perflenapent emulsion "could be used to detect intracardiac shunts or other congenital abnormalities," and "should

permit the use of echocardiography to visualize and localize myocardial perfusion defects."

7. Perflenapent emulsion "may be able to increase the accuracy of exercise echocardiography."

- The article by Steven Quay et al., "Safety Assessment of Perflenapent Emulsion for Contrast Enhancement of Echocardiography and Diagnostic Radiology Ultrasound Studies," is very similar to the article in Applied Radiology that describes the authors' view of the ideal agent and that EchoGen fulfills most of these criteria.

4. Slide Kit

In its slide kit, Sonus presents claims that EchoGen is safe and effective for prostate imaging, transcranial Doppler imaging, facilitation of diagnosis of hemangiomas, carotid artery blood flow, and determination of metastatic carcinoma.

5. Internet World Wide Web Site

On its' World Wide Web ("WWW") homepage, as of November 14, 1997, Sonus presents promotional claims regarding the effectiveness of EchoGen as follows:

- "The Company believes EchoGen offers significant benefits as a contrast agent including (I) small bubble size which allows EchoGen to pass through capillaries in the lungs and other organs, (ii) a long half life which will allow physicians a sufficient time to complete an EchoGen-enhanced ultrasound study, and (iii) intensity of the sound wave reflectivity or echogenicity providing for better quality images."

C. Conclusions and Requested Actions

Therefore, DDMAC requests that Sonus take prompt action to correct the violations discussed in this letter and prevent their recurrence. Because these violations include promotion of an investigational new drug to a large and varied audience (attendees at major scientific meetings, and unknown numbers of "hits" on its WWW site), Sonus should propose a comprehensive and multi-faceted action plan to disseminate corrective messages about the issues discussed in this letter.

DDMAC requests that these actions include:

1. The immediate cessation of dissemination of all promotional activities and materials that state or suggest that EchoGen is a safe and effective ultrasound contrast agent for echocardiography and radiology imaging.

2. Within (15) fifteen calendar days of the date of this letter (this letter is transmitted via facsimile), dissemination of a copy of this Warning Letter to all managers and representatives of Sonus, and to all Abbott marketing managers and representatives pursuant to co-marketing agreements or contracts for services.

3. Submit in writing Sonus' intent to comply with (1) and (2) and its plans for accomplishing corrective action.

4. The Sonus WWW homepage should be revised to delete all preapproval promotional messages.

5. Additional corrective actions to be determined by discussions between Sonus and DDMAC.

The violations cited and discussed in this letter are not intended to be a complete listing of all violations. We are evaluating other aspects of Sonus' promotional campaign for EchoGen and additional violations may be identified. DDMAC may request additional information in a separate correspondence to assist us with our evaluation of this matter. Consequentially, DDMAC may determine that additional remedial measures may be necessary to fully correct the false impressions resulting from Sonus' violative conduct.

Sonus' response should be received no later than April 9, 1998. If Sonus has any questions or comments, please contact Warren Rumble, Thomas Abrams, or Norman A. Drezin, Esq. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Sonus that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 6003 and NDA 20-372.

Failure to respond to this letter may result in regulatory action without further notice.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, R.Ph., JD
Director
Division of Drug Marketing,
Advertising and Communications